The standard for obviousness has been established over several years of court cases, such as *Graham v. John Deere*, 383 U.S. 1 148 USPQ 459 (1966), and has culminated in the guidelines set forth in §2141-§2164 of the MPEP to which the Office must adhere to when making a determination of obviousness.

According to MPEP §2142, an examiner must meet three basic criteria to establish a *prima facie* case of obviousness: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claim limitations.

As will be demonstrated below, one of skill in the art would not combine the teachings of Martin and Cao with any reasonable expectation of success. Further, Applicants respectfully submit that the Office has used impermissible standard for obviousness and has failed to successfully rebut Applicants arguments for non-obviousness.

The references fail to provide a reasonable expectation of success

An identical rejection was asserted in the first Office Action. In response to this rejection, the Applicants argued that the Examiner has not established a *prima facie* case of obviousness. The Examiner assumes that one of ordinary skill in the art would have been motivated to combine the bacterial polymerase of Cao et al. with the reagents and methods of Martin et al. However, the Applicant submits that the combination of the cited references would not have provided one of ordinary skill in the art with a reasonable expectation of success. As was understood by one of ordinary skill in the art at the time the invention was made, the use of prokaryotic [*Escherichia coli*] poly(A) polymerase to attach end-label ribonucleic acids with non-radioactive labels was believed to be impossible. For example, Rosemeyer et al. (U.S. Patent No. 5,573,913; issued November 12, 1996.) states:

> "The attachment of nucleotides to the 3' end of RNA molecules using...[*Escherichia coli*] poly(A) polymerase does...have considerable problems.... The efficient labelling of 3' ends of RNA molecules with [*Escherichia coli*] poly(A) polymerase is limited to the use of ATP and ATP derivatives since bases other than A are accepted much more poorly by the enzyme. Oligonucleotides have an extremely low efficiency as acceptor molecules. **The attachment of oligoribonucleotides to the 3' end of RNA molecules by [*Escherichia coli*] poly(A) polymerase is not known. It is not possible to attach non-radioactively labelled nucleotides**.... Therefore no process is known from the state of the art with which RNA molecules that are already

present can be provided in a simple manner with one or several non-radioactive marker groups."
[Column 1, line 58 through column 2, line 54.]

As shown by Rosemeyer et al., those of skill in the art did not believe it was possible to use a prokaryotic poly(A) polymerase to end-label a ribonucleic acid with a non-radioactively labeled ribonucleotide. Thus, any attempt to do so by combining the cited references of Martin et al. and Cao et al. would not have been made with a reasonable expectation of success.

Furthermore, as discussed in the previous response, Cao only teaches that bacterial (Escherichia coli) poly(A) polymerase has a potential use in mRNA polyadenylation. There is no mention in Cao et al. of the polyadenylation of RNA using non-radioactively labeled ribonucleotides. In contrast, the present application is directed to the end-labeling of ribonucleic acids with non-radioactively labeled ribonucleotides, of which Cao et al. is silent. Accordingly, the combined references of Martin et al. and Cao et al. fail to provide one of ordinary skill in the art with any reasonable expectation of success because the references fail to teach or suggest that a prokaryotic poly(A) polymerase could be used to end-label ribonucleic acids with non-radioactively labeled ribonucleotides.

Furthermore, as discussed in the previous response, there are many important differences between eukaryotic and prokaryotic poly(A) polymerases. For example, as is described in Sarkar, (Annu. Rev. Biochem (1997) 66:173-97), prokaryotic poly(A) polymerases do not require an upstream consensus sequence such as the AAUAAA sequence, as is required by eukaryotic poly(A) polymerases (Sarkar, pp. 182 and 193); the poly(A) tracts of prokaryotic mRNAs are significantly shorter than those of eukaryotic mRNAs (Sarkar, pg. 175); and only a relatively small fraction of mRNA molecules are polyadenylated in prokaryotes, "in contrast to the virtually quantitative polyadenylation of most eukaryotic mRNAs." (Sarkar, pg. 175). Accordingly, the substitution of the prokaryotic poly(A) polymerase of Cao et al. into the method of Martin et al. of non-radioactive end-labeling RNA using a eukaryotic poly(A) polymerase, would not have provided one of ordinary skill in the art with any reasonable expectation of success because of the significant differences between eukaryotic and prokaryotic poly(A) polymerases and the numerous other differences between eukaryotic and prokaryotic intracellular systems as was generally known in the art at the time the invention was made.

Thus, the difficulties encountered by past researchers coupled with the significant differences between prokaryotic and eukaryotic poly(A) polymerases, would not have permitted one of ordinary skill in the art to combine the teachings of Martin et al. (fluorescent end-labeling of the 3'-end of RNA using eukaryotic poly(A) polymerase) and Cao et al. (mRNA polyadenylation using bacterial poly(A) polymerase) with any reasonable expectation of success. It was not until after the time of the Applicant's work, as reported in the present application, that one of ordinary skill in the art would have had a reasonable expectation of success in attaching non-radioactively (fluorescently) labeled ribonucleotides to the 3' end of ribonucleic acids with prokaryotic poly(A) (bacterial) polymerase.

As the Examiner has stated in this Office Action "Applicant is hereby notified that function of an enzyme and end-labeling of a substrate of that enzyme are two completely different phenomenon. In view of the Examiner's comments, how would one of skill in the art, knowing the biological function of a bacterial poly(A) polymerase be able to predict that the it would be able to end-label a substrate if the function of an enzyme and end-labeling of a substrate of that enzyme are two completely different phenomena? The Applicants respectfully submit that the Examiner's statement fully supports the Applicants' position that one of skill in the art would not be able to make such a prediction.

As previously asserted, the claimed kits are not *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because one of ordinary skill in the art would not have coupled the prokaryotic poly(A) polymerase with the non-radioactively labeled ribonucleotide in a kit for use in end-labeling ribonucleic acids, due to a lack of a reasonable expectation of success in using the two reagents together for any purpose.

The Office uses an impermissible standard for obviousness and has failed to successfully rebut Applicants arguments

In rebutting the Applicants's arguments in response to the rejection of the first Office Action, the present Office Action stated "This argument is not persuasive, especially in the presence of strong motivation provided by Cao et al since Cao et al states, "The identification of the gene for the second *E. coli* poly(A) polymerase opens the way for the detailed investigation of the metabolic role of mRNA polyadenylation by studying the consequences of disruption of either or both of the poly(A) polymerase genes (Page 11585, Column 2, last sentence"."

The Applicants respectfully assert that the Office has used an impermissible standard in making this obviousness rejection. Further, the Applicants respectfully assert that the Office has provided no evidence to rebut the Applicant's previous arguments and show that the subject invention is obvious.

The Courts (*In re O'Farrell*, 853 F.2d 894, 903 7 USPQ2d 1673 1681 (Fed. Cir. 1988)) and the MPEP (§ 2145X.B) very clearly state that an invitation to "explore a new technology or general approach that seemed to be a promising field of experimentation" is not the standard that is used for obviousness. Such a standard "would not only be contrary to statute but result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of "research"." *In re Tomlinson* 363 F.2d 928, 150 USPQ 623 (CCPA 1966). As such, the test of obviousness is therefore not a determination of what prior art would have led a skilled person *to try*. In other words, any obviousness rejection that is based on an invitation to "explore a new technology…that seemed to be a promising field of experimentation" is based on an impermissible standard for obviousness.

In establishing this rejection and in rebutting the Applicants' arguments, the Office states that motivation to use Cao's prokaryotic poly(A) polymerase in the methods of Martin is found in Cao, who states "The identification of the gene for the second *E. coli* poly(A) polymerase opens the way for the detailed investigation of the metabolic role of mRNA polyadenylation by studying the consequences of disruption of either or both of the poly(A) polymerase genes". The Office Action states that one of skill in the art would have combined Cao's polymerase into Martin's methods in order to further the investigation, and, as such, one of skill in the art would have found motivation to combine the references. In other words, Cao states that the discovery of the second E. coli poly(A) polymerase gene "opens the way for a detailed investigation" of mRNA metabolism, and the Office Action submits that this investigation would lead to the claimed invention.

The Applicants respectfully submit that Cao's statement merely represents an invitation to perform a detailed exploration into mRNA metabolism using a bacterial poly(A) polymerase. This statement would not have led one of skill in the art to combine the references of Martin and Cao, and would not have led one of skill in the art towards the claimed invention. Cao's statement represents nothing more than an invitation to "explore a new technology or general approach that seemed to be a promising field of experimentation".

Because the Office has used a similar approach to establish the obviousness of Claims 27, 34, 35 and 42-44 as Claims 17-20, 24-26, 28-32 and 36-41, the Office has also used an impermissible standard for obviousness in this rejection.

Based on the foregoing, it is respectfully submitted that the Examiner has attempted to establish obviousness by determining what the prior art would have led a skilled person *to try*, rather than what the prior art would have let a skilled person *to do*. As such, the Office has not established a proper *prima facie* case of obviousness. Furthermore, as demonstrated in the Applicant's previous response, one of skill in the art would not combine the references with any reasonable expectation of success. Accordingly, this rejection of Claims 27, 34, 35 and 42-44 under 35 U.S.C. §103(a) may be withdrawn.

CONCLUSION

The Applicant respectfully submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Gordon Stewart at 650 485 2386. The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078.

Respectfully submitted,

Date: 2.3.03

By: _____
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